

REMARKS

After amendment, claims 1 and 3-27 remain pending, claim 2 being cancelled in order to advance prosecution of the instant application. Applicants note that any subject matter cancelled herein is cancelled *without prejudice* in order to give Applicants a chance to refile claims containing such subject matter in any subsequent divisional or continuation application. The amendment to the claims presented herein is supported by the originally filed application and claims. No new matter has been added by way of this amendment. It is respectfully submitted that amended claims address the Examiner's concerns and the application should be placed in condition for allowance.

The Examiner has variously objected to the originally filed claims or rejected the originally filed claims of the instant application under 35 U.S.C. §102(b) or §103 for the reasons stated in the September 19, 2008 office action. Applicants shall address each of the objections/rejections in the sections which are presented hereinbelow.

The Objection to Claims 12 and 13

The Examiner has objected to originally filed claims 12 and 13 for the reasons which have presented in the September 19, 2009 office action on page 2, points 3 and 4. In response, Applicants have amended claims 12 and 13 to specifically address the Examiner's objections. With the amendment to claims 12 and 13, Applicants respectfully submit that the Examiner's objection has been addressed.

The Prior Art Rejections

The Examiner has rejected originally filed claims 1-27 variously under 35 U.S.C. §102(b) and 103 for the reasons which are stated in the office action on pages 2-13.

Applicants shall address each of the Examiner's rejections in the sections which are presented hereinbelow.

The Present Invention and Its Significance

The present invention is the first time that reliable differentiation between an LSD positive and non positive individual has been achieved using mass spectroscopic interrogation. Such differentiation has been achieved by analysis of the *profile* of lipid containing storage associated compounds from a tissue or body fluid sample of the person under test. The profile is more than just ascertaining whether one compound is present or absent or determining the levels at which the compound is present or determining the relative levels of two compounds. The present claim defines that the levels of three or more compounds need to be ascertained, thus reflecting the need to ascertain a lipid profile, and compare the profile of an individual against a datum.

Data in the Specification

The data in the specification shows that certain combinations of lipids allow for differentiation between all three of control individuals, heterozygotes and hemizygotes. Thus, as presented, figure 4A is a histogram showing this for Gaucher patients where four compounds are used, as a "ratio 4". The comparable data using two compounds as shown in figures 3A and 3B is unable to distinguish heterozygotes.

Similarly, figure 15 is a plot for Fabry patients where the levels of four compounds are used in a plot of CTH 24:1/CM C24:0 v LC C24:1/GC 24:0. This also gives good differentiation when compared to the differentiation shown in figures 14. Figure 25A is a plot for Fabry patients where the levels of four compounds are used in a plot of CTH 16:0/PC C36:4 v PS C16:1/PS C18:0_18:1. This also gives good differentiation, for all three statuses.

Further work

Further work has been undertaken by the inventors and further data in support of the proposition that the lipid profile is a good means for ascertaining the LSD status of an individual has been produced.

Applicants have enclosed a copy of Fuller *et al*, *Clinical Chemistry* 51:4; 688 - 694 (2005) by the present inventors. The Examiner's attention is directed to page 693, figures 2 and 3, wherein 2A and 2B show a comparison of two lipid containing storage associated compounds, and 2C shows the comparison of four lipid containing storage associated compounds. It can be seen that there is a much clearer differentiation between the two states using four compounds compared to using two. Similarly figure 3 shows good differentiation using 4 markers.

A separate paper which is also enclosed for the review of the Examiner is Meikle *et al* *Blood Cells Molecules and Disease* (2008) May-June 40(3):420-7, also enclosed, incorporates 17 lipid species into an analysis and shows excellent differentiation. We refer the Examiner in particular to Figure 2A, and the paragraph bridging second column page 4, through to second column page 5.

The Rejection of Claims 1-9 As Being Anticipated by Fujiwaki

The Examiner has rejected originally filed claims 1-9 under 35 U.S.C. §102(b) as being anticipated by Fujiwaki, *Brain and Development*, 2002 ("Fujiwaki") for the reasons which are stated in the office action on pages 2-4. In response, Applicants respectfully submit that the presently pending claims are not anticipated by Fujiwaki.

The present invention has been described hereinabove and that description is referenced here. Applicants, in response, point out that Fujiwaki does not disclose the use of three or more

compound indicators to assess a LSD status of an individual, and therefore does not anticipate either claim 1 or 3. Applicants note that the language of claim 1 refers to ". . . using all of said compound indicators . . ." to measure an index number. The word "all" positively defines that at least three compounds are used to calculate an index number. There is nothing in Fujiwaki that refers to the use of three compounds in any calculation or graphic representation of a value and consequently, it cannot reasonably be asserted that Fujiwaki somehow anticipates the present invention.

Claim 2 has been cancelled and claims 4 through 9 are dependent on claims 1 and 3, which are not anticipated for the reasons set forth above. Consequently, claims 4 through 9 are also not anticipated by Fujiwaki.

For the reasons presented, it is respectfully submitted that the presently pending claims are not anticipated by Fujiwaki.

The Obviousness Rejections

The Examiner has rejected 10-16, 23, 25, 17-22, 24, 26 and 27 variously over Fujiwaki, Whitfield, et al., *Molecular Genetics and Metabolism*, 2002 ("Whitfield"), Cable, et al., *Neurology*, 1982 ("Cable") and Aerts, et al., *Journal of Inherited Disease*, 1993, vol. 16, pages 288-291 ("Aerts") for the reasons which are set forth in the September 19, 2008 office action on pages 5-13. For the reasons which are set forth in detail hereinbelow, Applicants respectfully submit that the present invention is not disclosed by any one or more the references which have been cited against the present invention.

It is submitted that the present invention set forth in pending claims 1 and 3-27 is non-obvious, in light of the prior art relied on by the Examiner. None of the citations raised or any

prior art known to the applicant or inventors discloses or suggests that more than two indicator compounds could possibly provide adequate differentiation to detect heterozygous individuals from either homozygous individuals or controls.

Prior to the present invention, there was simply no way of knowing that the use of three compounds in the comparison would distinguish between heterozygotes and controls better than the use of the two controls as a result of what turns out to be a cumulative effect of the distinctions made by analysis of the individual levels. There had never been any suggestion that combining more than two lipid levels would provide better distinguishing ability. What is suggested by the prior art is that for a more accurate result one or two lipid compound levels should be used as an adjunct to another method (such as enzyme level, or the measure of LAMP-1) to achieve an enhanced result. The prior art thus teaches away from combining measurements of the levels of three or more lipid containing compounds to achieve a better result. The result of better distinction was therefore not predictable, nor was there any motivation to combine the levels of more than two compounds in the calculation of an index number.

The Prior Art

Summary of the Prior art

Fujiwaki

The Examiner states that Fujiwaki discloses "estimating a level in the sample of each of three or more compound indicators . . . calculating an index number using the ratio of ceramide/sphingomyelin and ceramide monohexoylceramide."

Claim 1 and 3 define the step of "calculating an LSD index number using all of the compound indicators". Our submission is that Fujiwaki does not calculate an index number using all three compound indicators. Moreover, there is no suggestion that the use of two ratios is better than the use of one ratio. In fact it is cogent contention of Applicants that Fujiwaki only measures one LSD compound, for example with Fabry Disease merely observing that ceramide is

higher. See page 171, column 15th Paragraph of Fujiwaki.

The ratios referred to are each just a measure of a single compound, which in the case of Fabry Disease (FD) is ceramide. The comparison with sphingomyelin or monohexosylceramide is simply to adjust the values obtained to that of an internal control. As the Examiner will readily appreciate, internal controls are necessary because samples taken from any given person, in this case a control or the FD sufferer will have slightly different treatments or have been applied in smaller or lesser amounts. The finding that the ceramide/sphingomyelin ratio and the Ceramide / monohexosylceramide ratio is higher in FD patients is simply used to standardize the result. The closing remark on page 171 left column 5th paragraph illustrates this where the authors state "These findings indicated the accumulation of ceramide in this patient". There is no suggestion in Fujiwaki that the three compounds, i.e., ceramide, sphingomyelin and monohexosylceramide should be used produce an index figure reflecting all three compounds, nor is there any suggestion or conclusion that taken together variation of three different compounds can provide a more relevant indicator than two or indeed one.

With respect to the GD patient, only one internal control is used- thus, monohexosylceramide levels are compared to sphingomyelin. This is a similar methodology as is used in Whitfield as described on pp 47 2nd paragraph (internal standards) and page 49 1st column 2nd and 3rd paragraph (quantification of GC and LC), except that the Whitfield text refers to the species of interest when compared to the standard.

It is respectfully submitted that there is therefore no support for the Examiner's statement that Fujiwaki suggests calculating an index using a comparison of levels of 3 compounds relative to a datum.

Whitfield

This citation attempts to provide a better diagnostic method including the use of lipid containing compounds, and other markers. In Whitfield, the investigators looked at ratios of two different LSD associated compounds and, as particularly relevant for the present invention, the ratio of 16:0 glucosylceramide / 16:0 lactosylceramide.

Whitfield does not obviate the deficiencies of Fujiwaki in failing to render the present invention obvious. In Whitfield, there is no suggestion that the use of a lipid profile or the use of three or more lipid containing compounds would give sufficient resolution to distinguish between hemi and heterozygous individuals. Nor is there a suggestion of refining the lipid analysis in any way; rather the authors suggest that what should happen is that several indicators be used. Thus at page 53 starting on last two lines, Whitfield writes: "These findings support the concept of a multifaceted approach for investigating the progression of Gaucher disease and it is anticipated that these methods will be employed to supplement established techniques currently used in the diagnosis and evaluation of patients with Gaucher disease and in the monitoring of therapy." In Whitfield, there is accordingly no suggestion that the measurement of lipid compounds levels on their own will not be enough to discriminate the LSD statuses of an individual, and nothing that suggests use of the levels of 3 or more lipid containing compounds rather than indicators of a differing chemical origin should be used. It is respectfully submitted that Whitfield actually teaches away from the present invention.

Cable

Cable shows that trihexosyl ceramide (CTH) and Digalactosyl ceramide (Digal-Cer) increase in heterozygotes with Fabry Disease. The ratio of CTH and Digal-Cer to hydroxyfatty acid Glucosyl Ceramide (GC) was increased. In Cable, again GC is used as an internal control (see page 1141 4th paragraph column 1) because "... the amount of this compound was similar in

both normal and Fabry heterozygote urine . ." See also page 1142 paragraph bridging column 1 and 2. Thus, Cable does not particularly refer to the use of levels of two or more compounds that vary between heterozygotes and normals individuals but uses the two compounds to give a standardized level of the individual compounds Digal-Cer and CTH.

In Cable, as with Whitfield, there is simply no suggestion that quantification of these compounds is suitable for use on their own, rather, that the quantification is useful in combination with enzyme level assessment. As state, "this method provides a useful adjunct to enzyme analysis of Fabry heterozygote detection because enzyme analysis alone does not permit confident heterozygote detection." In any event, the method employed in Cable is not adequate to provide the necessary differentiation of the present invention.

Aerts

There is no suggestion in Aerts that the levels of compounds concerned will provide for a means to distinguish heterozygotes from normal or hemizygotes, nor is there a suggestion that the additional use of Ceramide will further enhance the capacity to distinguish. Moreover, Applicants note that there is no indication in Aerts that a change in ceramide concentration actually occurs - there is only an expectation that it would. Further, there is also no motivation to use three or more compounds in calculating an index number for reasons set out above. In sum, Aerts is a deficient reference and fails to disclose or suggest the present invention.

We now turn our analysis to the Examiner's individual claims rejections and the impact that the prior art has on the present invention. Applicants respectfully submit that the presently claimed subject matter is non-obvious over the references as cited against the present invention.

The Rejection of Claims 10-16, 23 and 25 as Being Obvious Over Fujiwaki, in view of Whitfield

Regarding the Examiner's rejection of claims 10-16, 23 and 25 as being obvious over Fujiwaki, in view of Whitfield, Applicants cogently posit, that in the case of claim 10 – 16, the subject matter of these claims is non-obvious by reason of the use of at least three compounds in calculating the index number.

Regarding the rejection of claims 23 and 25, the Examiner states that "Applicant is advised that the rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art . . . In that regards Fujiwaki teaches comparing SM with GC for assessing Gaucher disease (see page 171m left col. 6th paragraph). Whitfield teaches comparing LC with GC for assessing Gaucher disease (see page 51m right column. 3rd paragraph). One of ordinary skill in the art could have combined the two methods as taught by Fujiwaki and Whitfield. In the combination (SM and LC compare with GC) each method (SM/GC or LC/GC) merely performs the same function (assess the status of the Gaucher disease) as it does separately. One of ordinary skill in the art would have recognised that the result of the combination were predictable."

Applicants respectfully submit that the combination of SM and LC compared with GC is more than the combination of SM/GC and LC/GC. In the present invention, the levels of three compounds are determined instead of two and the notionally cumulative result is enhanced relative to the individual result, giving usable differentiation between the different severity statuses of LSD. The prior art teaches that the use of a further indication, in addition to relative levels of lipid containing compounds, is necessary to give adequate differentiation between the different statuses of LSD patients, and that the use of lipid containing compounds alone is not an adequate measure, and accordingly that the usefulness of three compounds in place of two is not predictable use of three. Claims 23 and 25 use three compounds in making an assessment and

moreover define three specific compounds. It is submitted accordingly, that this assessment is not predictable.

Based upon the foregoing, Applicants respectfully submit that the subject matter of claims 10-16, 23 and 25 are non-obvious over the teachings of the cited prior art of Fujiwaki, in view of Whitfield.

The Rejection of Claims 17-22 as Being Obvious Over Fujiwaki, in View of Cable

Regarding the Examiner's rejection of claims 17 -22 as being obvious over Fujiwaki, in view of Cable, Applicants respectfully submit that the subject matter of these claims is non-obvious by reason of the use of at least three compounds in calculating the index number. There is no motivation to combine three or more compounds in calculating an index number in that there was no reason to believe that this would give a more reliable result.

Regarding the Examiner's rejection of claim 18, Applicants submit that the Examiner's contention that the combination of Fujiwaki and Cable show the calculation of an index number for Fabry by the use of two or more of Cer, LC and CTH compared to SM is not supported by a fair reading of the prior art, because the specific combination is not referenced in either document, nor is there a suggestion that other combinations of lipid compounds could be used.

Regarding the Examiner's rejection of claim 19, Applicants submit that, contrary to the Examiner's contention, the combination of Fujiwaki and Cable do not show the calculation of an index number for Fabry by the use of two or more of Cer, LC and CTH compared to GC because the specific combination as claimed is not referenced in either document. These claims are non-obvious over the prior art teachings.

Turning to the Examiner's rejection of claim 20 and 21, Applicants submit that, contrary

to the Examiner's contention, picking particular species of compounds to analyse is not simply a routine optimization. There is nothing in the prior art to suggest that any particular species of lipid containing compounds would be more elevated than any other species of the compound. The claims present a new characteristic that provides an enhanced result, and is not just an adjustment of earlier disclosed characteristics. These claims are non-obvious over the prior art teachings.

Regarding the Examiner's rejection of claim 22, it is Applicant's submission that it was non-obvious to combine the values of three or more compounds and certainly non-obvious to combine them in the combination set out in this claim., especially given that the prior art *teaches away* from the concept that determining a greater number of lipid compounds in an attempt to make the measurement of these lipid compound provide for an index number with greater capacity to distinguish between heterozygotes and normal individuals. The greater capacity to distinguish is, it is submitted, is not a predictable result and is a patentable feature over the teachings of the prior art.

Based upon the foregoing, Applicants respectfully submit that the subject matter of claims 17-22 are non-obvious over the teachings of the cited prior art of Fujiwaki, in view of Cable.

The Rejection of Claims 24 and 26 as Being Obvious Over Fujiwaki, in View of Whitfield and further in view of Aerst

The deficiency of the teachings of Fujiwaki, in view of Whitfield have been described in great detail hereinabove and are referenced here. It is noted that there is absolutely no suggestion in Aerts that the levels of compounds concerned will provide for a means to distinguish heterozygotes from normal or hemizygotes, nor is there a suggestion in Aerts, Whitfield or Fujiwaki that the additional use of Ceramide will further enhance the capacity to distinguish

these forms. The features of the present invention in claims 24 and 26 clearly distinguish over the teachings of the cited prior art. Moreover, Applicants further note that there is absolutely no indication in Aerts that a change in ceramide concentration actually occurs - there is only an expectation that it would. There is also no motivation to use three or more compounds in calculating an index number for reasons set out above. Consequently, it is respectfully submitted that claims 24 and 26 are non-obvious over the cited prior art.

The Rejection of Claim 27 as Being Obvious Over Whitfield, in view of Fujiwaki

Applicants note that originally filed claim 27 has been amended such that the formulation step comprises " . . . formulating a combination of three or more . . . indicators by which to calculate an index number". The amendment brings the claim in conformity with claims 1 and 3, discussed *supra*, and Applicants respectfully submit that claim 27 is non-obvious over the cited because it specifies the use of three or more indicators in the calculation of an index number, in complete contrast to the cited art as set forth above. It is respectfully submitted that amended claim 27 is patentable over the cited prior art.

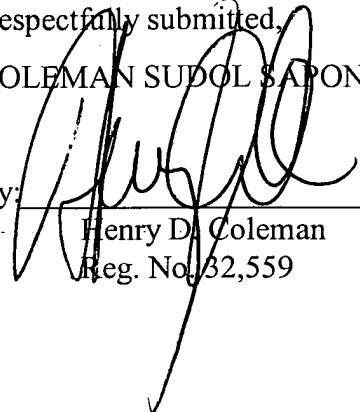
For the reasons which have been presented in great detail hereinabove, it is respectfully submitted that the presently claimed invention now complies with the requirements of 35 U.S.C.. Favorable consideration of this application is respectfully solicited.

For all of the above reasons, it is respectfully submitted that the present application is now in condition for allowance and such action is earnestly solicited. 1 claim has been cancelled (claim 2) and no new claims have been added to the present invention. No fee is therefore due for the presentation of this amendment. A petition for an extension of time is enclosed as is the appropriate fee.



The Commissioner is authorized to charge any fee due or credit any overpayment to deposit account 04-0838.

Respectfully submitted,
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